DETAILED ACTION

Response to Amendment

1. Claims 15-18 have been amended as requested in the amendment filed on February 28, 2008. Following the amendment, claims 1-18 are pending in the instant application.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-3 and 15-18, in the reply filed on February 28, 2008 is acknowledged. The traversal is on the ground(s) that the Benaud art applied in arguments for lack of unity does not constitute prior art in light of priority claim to US provisional Application 60/444,475. Examiner notes that this provisional application was missing from the Bibliographic data sheet and this error has been remedied in PALM and the Image File Wrapper. However, lack of prior art showing notwithstanding, the request for withdrawal of the restriction requirement is not found persuasive because pursuant to 37 C.F.R. § 1.475 (a), Unity of invention before the International Searching Authority, an international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, pursuant to 37 C.F.R. § 1.475 (b), the ISA/US considers that unity of invention exists if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

The inventions of Groups I-VI are drawn to different processes, screening assays and compound products each of which are patentably different categories of inventions that do not fall into one of the combinations that the ISA/US considers as supporting unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 28, 2008.

4. Claims 1-3 and 15-18 will be examined upon their merits in the instant Office action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 is vague in that it recites “administering to an individual an inhibitor of annexin 2 or a complex of annexin2 and caveolin1”. It is unclear if the claim is meant to recite administering a complex of annexin 2 and caveolin 1, or if the claim recites administration of either an inhibitor of annexin 2 or an inhibitor of the formation of a complex between annexin 2 and caveolin 1.

8. The term "reduces" in claim 2 is a relative term which renders the claim indefinite. The term "reduce" is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claim is further vague and indefinite in that the method requires reducing "the activity of annexin 2", but the claim does not specify what specific activity is reduced, nor does the claim recite method steps for ascertaining a reduction in any activity. Therefore, one of ordinary skill in the art would not be reasonably apprised as to the metes and bounds of the invention.

9. Claims 3 and 15-18 are indefinite for depending from indefinite claims.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-3 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites in the alternative "an inhibitor of annexin 2 or a complex of annexin 2 and caveolin 1". Claim 2 recites in the alternative "an agent which reduces the activity of annexin 2 or a complex of annexin 2 and caveolin 1". Claim 3 further limits Claim 2 by recitation that if the agent reduces the activity of the complex, it does so "by disrupting complex formation". Claims 15 and 17 define the "inhibitor" or "agent" as a nucleic acid molecule that serves the function of blocking gene expression. Claims 16 and 18 define the "inhibitor" or "agent" as a morpholino oligonucleotide. However, the claims do not require that the "inhibitors" or "agent" possess any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of molecules that is defined only by function and the instant specification fails to describe the entire genus of molecules that are encompassed by these claims.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant is in possession of specific examples of annexin 2 morpholino oligonucleotides (page 18, paragraph 0062). The claims, however, encompass methods comprising the administration of any inhibitor of annexin 2 or a complex of annexin 2 and caveolin 2, thus, the claims are not limited to specific molecules with known structure. The claims merely require the claimed methods

employ molecules that serve to reduce the activity of annexin 2 or a complex of annexin 2 and caveolin 1, or disrupting complex formation.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claim is a recitation of activity. There is not even identification of any particular portion of the structure that must be conserved for activity. As stated above, it is not even clear what molecules are considered inhibitors or agents. The art teaches a wide range of annexin 2 inhibitors such as chemical inhibitors (Liu et al. European Journal of Biochemistry, 269:4277, September 2002), tyrosine kinase inhibitors (Zhao et al. Journal of Biological Chemistry, 278(6): 4205-4215, November 12, 2002) and monoclonal antibodies (Pietropaolo et al. Journal of Virology, 71(12):9803-9807, December 1997) but the specification does not provide a complete or partial structure of those inhibitors or agents that fulfill the functional requirements of the claims, and the specification fails to provide a representative number of species for the recited genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, the court clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date

sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of annexin 2 inhibitors or agents of the claims, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identifying activity. Adequate written description requires more than a mere recitation of activity as part of the invention and a reference to a potential method of isolating or screening those compounds that serve that activity. The compound itself is required. See *Fiers v Revel*, 25 USPQ2d 1601 at 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification only provided for the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

12. Claims 1-3 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cholesterol uptake in the gut and lowering levels of cholesterol and cholesteryl ester in zebrafish embryos wherein that method comprises the administration of the specific morpholino oligonucleotide *anx2b* (Figure 5C), does not reasonably provide enablement for a method for inhibiting cholesterol uptake in the gut comprising administering in any other organism any other inhibitor of annexin 2 or inhibitor of the formation of a complex between annexin 2 and caveolin 1, nor is it enabling for a method of lowering levels of LDL cholesterol comprising administering an agent that reduces the activity of annexin 2 or reduces the activity of a complex of annexin 2 and caveolin 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-3 and 15-18 broadly encompass methods of inhibiting cholesterol uptake in the gut and lowering levels of LDL cholesterol comprising administering any inhibitory agent that reduces the activity of or reduces or inhibits a complex between annexin 2 and caveolin 1. These are methods that are not obvious variants of one another, for examples methods that inhibit cholesterol uptake in the gut do not necessarily lead to lower levels of LDL cholesterol. It is well-known in the art that only 25% of blood cholesterol comes from ingested food, the other 75% is made within the body and is influenced by genetic factors. The claims, however, broadly encompass methods of lowering cholesterol uptake and circulating LDL cholesterol levels, with a reasonable expectation of success, in any individual. Furthermore, the claims are

broadly drawn to methods comprising administration of any "inhibitor" or "agent" that reduces the activity of annexin 2 or the complex between annexin 2 and caveolin 1.

The invention is based on the finding that CAV1 and ANX2 form a heterocomplex within the intestines that plays a role in cholesterol uptake across the zebrafish embryo gut (page 24, ¶ 0080). The inventor commercially obtain morpholino oligonucleotides (MOs) against caveolin 1 and annexin 2 sequences and hypothesis that these MOs will serve to block ANX2b and CAV1 protein synthesis and regulate levels of heterocomplex formation and heterocomplex function as it pertains to cholesterol uptake. However, the instant specification is not found to be enabled for the method as claimed, for the following reasons. The instant specification does not provide enough guidance to one of ordinary skill in the art, nor working examples, which would show that the claimed method was successfully achieved. Absent such guidance, one of ordinary skill in the art would require undue experimentation to discover how to practice Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention relates to the blocking of the formation of an intestinal heterocomplex between annexin 2 and caveolin 1. The instant specification identifies

that the in vivo administration of the morpholino oligonucleotide *anx2b* (SEQ ID NO: 12) in zebrafish embryos leads to a reduction in the accumulation of cholesterol in the digestive tract and leads to significantly lower levels of cholesterol and cholesteryl ester in injected embryos.

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-1], which states: "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that it allows for the inhibition of cholesterol uptake in the gut and reduction of LDL cholesterol levels in any individual comprising the administration of any inhibitor or annexin 2 or any inhibitor of a complex between annexin 2 and caveolin 1, or the administration of any agent that reduces annexin 2 activity or any agent that reduces the activity of the heterocomplex between annexin 2 and caveolin 1. As opposed to the claims, what is

disclosed about the claimed method is narrow: The working examples provide guidance only as to the inhibition of cholesterol uptake and lowering of cholesterol and cholesteryl ester levels in zebrafish embryos comprising the administration of a single specific morpholino oligonucleotide encoded by SEQ ID NO: 12. The specification provides no direction or guidance as how the method is to be practiced *in vivo*, with a reasonable expectation of success in any other species, or with any other inhibitor or agent.

The state of the art at the time of filing recognized that CAV1 and ANX2 play a role in intracellular sterol trafficking (Uittenbogaard et al. *J Biol Chem*, 2002, cited as Reference 9 on page 26 of the specification and Reference C2 on the IDS filed April 19, 2006). While the skill level in the art is high, the level of predictability is low. As stated above, nitric oxide chemical inhibitors, tyrosine kinase inhibitors and monoclonal antibodies were known in the art to modulate annexin 2, but there is no guidance within the art or within the instant specification as to how to practice the claimed methods with a reasonable expectation of success comprising administration of any of these molecules. Furthermore, Applicants own data demonstrate the unpredictability of morpholino oligonucleotides as used in the method. While the in vivo administration of the MO *cav1* serves to inhibit CAV1 protein production and leads to only monomeric ANX2b (page 22, paragraph 0075), thereby reducing the formation and activity of the intestinal heterocomplex, in vivo cholesterol uptake "experiments using cav1 MO were not possible because injected larvae sow early developmental abnormalities including defects in axis elongation and somite patterning … and failed to survive to a stage where NBD-cholesterol is ingested" (page 23, paragraph 0077). Thus, in Applicants

own example, not every inhibitor or agent that serves to block complex formation or activity, is successfully used in the method as claimed. Thus, the claims are not enabled commensurate in scope with these claims.

The standard of an enabling disclosure is not the ability to make and test if an invention works but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is

(571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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